Remarks

Applicants request consideration on the merits of the above-referenced patent application.

I. Amendments to the Specification

In accordance with 37 CFR §1.78 and MPEP §202.01, the first paragraph in the specification has been amended to identify the patent application to which this patent application is claiming priority.

Paragraphs 5, 13-15, 20, 329, 333, 337, and 389 have been amended to correct various cites. Applicants submit that these amendments correct obvious errors, and are therefore permissible under MPEP §2163.07. Applicants further submit that these amendments are supported by the cited references themselves.

Paragraphs 14, 16, 20, 21, 33, 78-81, 83, 86, 277, 328, and 335 have been amended to replace "hydroxamate" with "hydroxamic acid". In addition, Paragraph 2 and the abstract (on page 195) have been amended to indicate that the term "hydroxamic acid" includes hydroxamates. Applicants submit that these amendments simply rephrase the specification, and are therefore proper under MPEP §2163.07. They also are supported by, for example, Applicants' description of the compounds throughout the specification.

Paragraph 79 has been amended to include aggrecanase as a target of the compounds of this invention. Applicants submit that this amendment is supported throughout Applicants' specification. Such support includes, for example, paragraph 28 on page 10.

Other amendments simply rephrase the specification, remove redundancies or unnecessary terms, or correct grammatical or obvious errors. Applicants submit that such amendments are permissible under MPEP §2163.07.

II. Amendments to the Claims

This Amendment A cancels claims 9-13, 16-25, 27, 28, 32, 33, 36-40, 42-46, 48, 49, 55, 56, 63, 67, 68, 70, 71, 74-78, 89, 90, 92-95, and 100-104, and adds new claims 111-113. Thus, claims 1-8, 14, 15, 26, 29-31, 34, 35, 41, 47, 50-54, 57-62, 64-66, 69, 72, 73, 79-88, 91, 96-99, and 105-113 are pending.

Claims 1, 3, 14, 15, 29, 34, 50, 52, 57, 59, 60, 64-66, 69, 72, 73, 76, 79-82, 84-88, 91, 96-99, 106, and 108-110 have been amended. All the claims, including the amendments, are shown in the previous section. Applicants submit that the amendments do not introduce new matter. Specifically:

As the Examiner may recall, a restriction requirement was issued in the parent application on January 22, 2003. That restriction requirement split the claims into 6 groups. As noted below, Applicants wish to elect **Group I** for examination in this application. This group encompasses compounds having a tetrahydropyranyl group at the alpha-position (*i.e.*, compounds where Z is O). The structures and/or substituent definitions in claims 1, 3, 14, 15, 29, 34, 50, 52, 57, and 58 have been amended in accordance with this election.

Claims 59, 64, 69, 72, 79, 84, 91, and 96 have been amended to more clearly describe the condition being treated. This amendment simply rephrases the claims, and does not affect their scope or add new matter. Thus, it is permissible under MPEP §2163.07.

Claims 59, 64, 69, 72, 79, 84, 91, and 96 have been amended to remove "prevent" and "preventing" from the method description. This amendment clarifies the claims because it removes a redundancy, given that "treating a condition" encompasses "preventing a condition". More specifically, the phrase "treating a condition" means treating a pathological condition. "Preventing a condition", on the other hand, means reducing the risk of (or delaying) the onset of a pathological condition in a subject pre-disposed to having the condition. *See* Applicants' specification, page 26, paragraph 77. Such a pre-disposition, however, is itself also a pathological condition. Thus, "preventing" one condition is "treating" an earlier condition, *i.e.*, the pre-disposition. This amendment therefore simply rephrases the claims, and does not affect their scope or add new matter. Thus, it is permissible under MPEP §2163.07.

The amendments to claims 60, 65, 73, 80-82, 85-87, 97-99, 106, and 108-110 amend the claims having multiple references to other claims so that they refer to only one other claim. In each instance, the removed claim reference has been replaced with the subject matter of the claim to which the reference referred.

Other amendments correct obvious or grammatical errors, or simply rephrase the claims. Such amendments are permissible under MPEP §2163.07.

Applicants submit that new claim 111 is supported by Applicants' specification at, for example, Example 362 on page 137.

Applicants submit that new claims 112-113 are supported by Applicants' specification at, for example, page 25, paragraph 74.

III. Scope of Pending Claims

All the pending claims are directed to compounds having a tetrahydropyranyl group at the alpha-position (*i.e.*, compounds where Z is O), treatment methods using such compounds and salts, or compositions comprising such compounds and salts. As noted above, this subject matter falls within **Group I** of the January 22, 2003 restriction requirement in the parent patent application. Applicants request that the Examiner use the compound recited in **claim 111** (*i.e.*, Example 362 on page 137) as the starting point for examination. Applicants also request that the Examiner use **osteoarthritis** as the starting point for examination of the method-of-treatment claims.

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Applicants submit that the pending claims are in condition for allowance. Applicants have enclosed a check to cover the filing fee of this application. Applicants do not believe that they owe any additional fee in connection with this filing. If, however, Applicants do owe any such additional fee(s), the Commissioner is hereby authorized to charge the fee(s) to Deposit Account No. **08-0750**. In addition, if there is ever any other fee deficiency or overpayment under 37 C.F.R. §1.16 or 1.17 in connection with this patent application, the Commissioner is hereby authorized to charge such deficiency or overpayment to Deposit Account No. **08-0750**.

The Examiner is requested to call the undersigned if any questions arise that can be addressed over the phone to expedite examination of this application.

Respectfully submitted,

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Appendix A
Marked-Up Version of Amendments to Specification

Paragraph 1 on page 1 has been amended in the following manner:

[1] This patent claims priority as a **as a divisional of U.S. Patent Application Serial No. 09/989,943 (filed November 21, 2001), which, in turn, claims priority as a** continuation-in-part to U.S. Patent Application Serial No. 09/570,731 (filed May 12, 2000), which, in turn, claims priority to U.S. Patent Application Serial Nos. 09/311,837 (filed May 14, 1999) and 09/256,948 (filed February 24, 1999), which, in turn, claim priority to U.S. Patent Application Serial Nos. 09/191,129 (filed November 13, 1998), 09/186,410 (filed November 5, 1998), 60/066,007 (filed November 14, 1997), 60/095,347 (filed August 4, 1998), 60/095,501 (filed August 6, 1998), and 60/101,080 (filed September 18, 1998). The entire texts of the above-referenced patent applications are incorporated by reference into this patent.

Paragraph 2 on page 1 has been amended in the following manner:

[2] This invention is directed generally to proteinase (also known as "protease") inhibitors, and, more particularly, to aromatic sulfone ~~**hydroxamate compounds (also known as "aromatic sulfone**~~ hydroxamic acid compounds **[["]]** **(including hydroxamates)** and salts thereof (particularly pharmaceutically acceptable salts) that, *inter alia,* inhibit matrix metalloproteinase (also known as "matrix metalloprotease" or "MMP") and/or aggrecanase activity. This invention also is directed to pharmaceutical compositions of such compounds and salts, and methods of using such compounds and salts to prevent or treat conditions associated with MMP and/or aggrecanase activity, particularly pathological conditions.

Paragraph 5 on page 2 has been amended in the following manner:

[5] Matrix metalloproteinases, a family of zinc-dependent proteinases, make up a major class of enzymes involved in degrading connective tissue. Matrix metalloproteinases are divided into classes, with some members having several different names in common use. Examples are: MMP-1 (also known as collagenase 1, fibroblast collagenase, or EC 3.4.24.3); MMP-2 (also known as gelatinase A, 72kDa gelatinase, basement membrane collagenase, or EC 3.4.24.24), MMP-3 (also known as stromelysin 1 or EC 3.4.24.17), proteoglycanase, MMP-7

(also known as matrilysin), MMP-8 (also known as collagenase II, neutrophil collagenase, or EC 3.4.24.34), MMP-9 (also known as gelatinase B, 92kDa gelatinase, or EC 3.4.24.35), MMP-10 (also known as stromelysin 2 or EC 3.4.24.22), MMP-11 [[1 I]] (also known as stromelysin 3), MMP-12 (also known as metalloelastase, human macrophage elastase or HME), MMP- 13 (also known as collagenase 111), and MMP- 14 (also known as MT1-MMP or membrane MMP). *See, generally*, Woessner, J.F., "The Matrix Metalloprotease Family" in *Matrix Metalloproteinases*, pp.1-14 (Edited by Parks, W.C. & Mecham, R.P., Academic Press, San Diego, CA 1998).

Paragraph 5 bridging pages 3 and 4 has been amended in the following manner:

[8] Inhibiting TNF (and related compounds) production and action is an important clinical disease treatment. Matrix metalloproteinase inhibition is one mechanism that can be used. MMP *(e.g.,* collagenase, stromelysin, and gelatinase) inhibitors, for example, have been reported to inhibit TNF-α release. *See, e.g.,* Gearing et al. *Nature*, 370 [[376,]] 555-557 (1994). *See also*, McGeehan et al. ~~*See also*~~, *Nature*, 370, [[376]], 558-561 (1994). MMP inhibitors also have been reported to inhibit TNF-α convertase, a metalloproteinase involved in forming active TNF-α. *See, e.g.,* WIPO Int'l Pub. No. WO 94/24140. *See also*, WIPO Int'l Pub. No. WO 94/02466. *See also*, WIPO Int'l Pub. No. WO 97/20824.

Paragraph 13 on page 5 has been amended in the following manner:

[13] A wide variety of thiol compounds have been reported to inhibit MMPs. *See, e.g.,* ~~W095/12389~~ WO 95/13289. *See also*, [[W0]] WO 96/11209. *See also*, U.S. Patent No. 4,595,700. *See also*, U.S. Patent No. ~~6,013,649~~ 6,013,649.

Paragraph 14 on page 5 has been amended in the following manner:

[14] A wide variety of ~~hydroxamate~~ hydroxamic acid compounds also have been reported to inhibit MMPs. Such compounds reportedly include ~~hydroxamates~~ hydroxamic acids having a carbon backbone. *See, e.g.,* WIPO Int'l Pub. No. *WO* 95/29892. *See also*, WIPO Int'l Pub. No. WO 97/24117. *See also*, WIPO Int'l Pub. No. WO 97/49679. *See also*, European Patent No. EP 0 780 386. Such compounds also reportedly include ~~hydroxamates~~ hydroxamic acids having peptidyl backbones or peptidomimetic backbones. *See, e.g.,* WIPO Int'l Pub. No.

WO 90/05719. *See also*, WIPO Int'l Pub. No. WO 93/20047. *See also*, WIPO Int'l Pub. No. WO 95/09841. *See also*, WIPO Int'l Pub. No. WO 96/06074. *See also*, Schwartz et al., Progr. *Med. Chem.*, 29:271-334(1992). *See also*, Rasmussen et al., *PharmacoL Ther.*, 75(l): 69-75 (1997). *See also*, Denis et al., *Invest New Drugs*, 15 **[[(3)]]**: 175-185 (1997). Sulfamato ~~**hydroxamates**~~ **hydroxamic acids** have additionally been reported to inhibit MMPs. *See*, WIPO Int'l Pub. No. WO 00/46221. And various aromatic sulfone ~~**hydroxamates**~~ **hydroxamic acids** have been reported to inhibit MMPs. *See*, WIPO Int'l Pub. No. WO 99/25687. *See also*, WIPO Int'l Pub. No. WO 00/50396. *See also*, WIPO Int'l Pub. No. WO 00/69821.

Paragraph 15 on page 5 has been amended in the following manner:

[15] It is often advantageous for an MMP inhibitor drug to target a certain MMP(s) over another MMP(s). For example, it is typically preferred to inhibit MMP-2, MMP-3, MMP-9, and/or MMP-13 (particularly MMP-13) when treating and/or preventing cancer, inhibiting of metastasis, and inhibiting angiogenesis. It also is typically preferred to inhibit MMP-13 when preventing and/or treating osteoarthritis. *See, e.g.*, Mitchell et al., J *Clin. Invest.*, 97**(3)**:761-768 (1996). *See also*, Reboul et al., *J Clin. Invest.*, 97**(9)**:2011-2019 (1996). Normally, however, it is preferred to use a drug that has little or no inhibitory effect on MMP-1 and MMP-14. This preference stems from the fact that both MMP-1 and MMP-14 are involved in several homeostatic processes, and inhibition of MMP-1 and/or MMP-14 consequently tends to interfere with such processes.

Paragraph 16 on page 6 has been amended in the following manner:

[16] Many known MMP inhibitors exhibit the same or similar inhibitory effects against each of the MMPs. For example, batimastat (a peptidomimetic ~~**hydroxamate**~~ **hydroxamic acid**) has been reported to exhibit IC_{50} values of from about 1 to about 20 nM against each of MMP-1, MMP-2, MMP-3, MMP-7, and MMP-9. Marimastat (another peptidomimetic ~~**hydroxamate**~~ **hydroxamic acid**) has been reported to be another broad-spectrum MMP inhibitor with an enzyme inhibitory spectrum similar to batimastat, except that Marimastat reportedly exhibited an IC_{50} value against MMP-3 of 230 nM. *See* Rasmussen et al., *Pharmacol. Ther.*, 75(l): 69-75 (1997).

Paragraph 20 on page 7 has been amended in the following manner:

[20] Various ~~**hydroxamate**~~ **hydroxamic acid** compounds have been reported to inhibit aggrecanase-1. Such compounds include, for example, those described in European Patent Application Publ. No. EP 1 081 137 A1. Such compounds also include, for example, those described in WIPO PCT Int'l Publ. No. WO **99/09000** ~~**00/09000**~~. Such compounds further include, for example, those described in WIPO PCT Int'l Publ. No. WO 00/59874.

Paragraph 21 bridging pages 7 and 8 has been amended in the following manner:

[21] In view of the importance of ~~**hydroxamate**~~ **hydroxamic acid** compounds and salts thereof in the prevention or treatment of several MMP- and/or aggrecanase-related pathological conditions and the lack of enzyme specificity exhibited by at least some of the ~~**hydroxamates**~~ **hydroxamic acids** that have been in clinical trials, there continues to be a need for ~~**hydroxamates**~~ **hydroxamic acids** having greater enzyme inhibition specificity (preferably toward MMP-2, MMP-9,MMP- 13, and/or aggrecanase, and particularly toward MMP-13 and/or aggrecanase), while exhibiting little or no inhibition of MMP activity essential to normal bodily function (*e.g.*, tissue turnover and repair). The following disclosure describes ~~**hydroxamate**~~ **hydroxamic acid** compounds and salts thereof that tend to exhibit such desirable activities.

Paragraph 33 bridging pages 11 and 12 has been amended in the following manner:

[33] In accordance with this invention, Applicants have found that certain aromatic sulfone ~~**hydroxamates**~~ **hydroxamic acids** tend to be effective toward inhibiting MMPs, particularly those associated with excessive (or otherwise pathological) breakdown of connective tissue. Specifically, Applicants have found that these ~~**hydroxamates**~~ **hydroxamic acids** tend to be effective for inhibiting MMP-2 MMP-9, and/or MMP- 13, which can be particularly destructive to tissue if present or generated in abnormally excessive quantities or concentrations. Applicants also have discovered that many of these ~~**hydroxamates**~~ **hydroxamic acids** tend to be effective toward inhibiting pathological aggrecanase activity. Applicants have further discovered that these ~~**hydroxamates**~~ **hydroxamic acids** tend to be selective toward inhibiting aggrecanase and/or MMPs associated with pathological condition conditions, and tend to avoid

excessive inhibition of MMPs (particularly MMP-1 and MMP-14) essential to normal bodily function *(e.g.,* tissue turnover and repair). Applicants have found, for example, that these ~~hydroxamates~~ **hydroxamic acids** tend to be particularly active toward inhibiting MMP-2, MMP-9, MMP-13, and/or aggrecanase activity in *in vitro* assays that are generally predictive of *in vivo* activity, while exhibiting minimal inhibition toward MMP-1 and/or MMP-14 in such assays. Examples of such *in vitro* assays are discussed in the example section below. Compounds (or salts) that are particularly useful as selective MMP inhibitors exhibit, for example, an *in vitro* IC_{50} value against one or more of MMP-2, MMP-9, and MMP-13 that is no greater than about 0.1 times the IC_{50} value against MMP-1 and/or MMP-14, more preferably no greater than about 0.01 times the IC_{50} value against MMP-1 and/or MMP-14, and even more preferably 0.001 times the IC_{50} value against MMP-1 and/or MMP-14.

Paragraph 71 bridging pages 23 and 24 has been amended in the following manner:

[71] Pharmaceutically-acceptable acid addition salts of the compounds of this invention may be prepared from an inorganic or organic acid. Examples of suitable inorganic acids include hydrochloric, hydrobromic acid, ~~hydroionic~~ **hydroiodic**, nitric, carbonic, sulfuric, and phosphoric acid. Suitable organic acids generally include, for example, aliphatic, cycloaliphatic, aromatic, araliphatic, ~~heterocyclyl~~ **heterocyclic**, carboxylic, and sulfonic classes of organic acids. Specific examples of suitable organic acids include acetate, trifluoroacetate, formate, propionate, succinate, glycolate, gluconate, digluconate, lactate, malate, tartaric acid, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilic acid, mesylate, stearate, salicylate, p-hydroxybenzoate, phenylacetate, mandelate, embonate (pamoate), ~~methanesulfonate,~~ ethanesulfonate, benzenesulfonate, pantothenate, ~~toluenesulfonate,~~ 2-hydroxyethanesulfonate, ~~sufanilate~~ **sulfanilate**, cyclohexylaminosulfonate, algenic acid, **[[b-]]** *β*-hydroxybutyric acid, galactarate, galacturonate, adipate, alginate, ~~bisulfate,~~ butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, dodecylsulfate, glycoheptanoate, glycerophosphate, ~~hemisulfate,~~ heptanoate, hexanoate, nicotinate, 2-naphthalesulfonate, oxalate, palmoate, pectinate, ~~persulfate,~~ 3-phenylpropionate, picrate, pivalate, thiocyanate, tosylate, and undecanoate.

Paragraph 72 on page 24 has been amended in the following manner:

[72] Pharmaceutically-acceptable base addition salts of the compounds of this invention include, for example, metallic salts and organic salts. Preferred metallic salts include alkali metal (group Ia) salts, alkaline earth metal (group IIa) salts, and other ~~**physiological**~~ **physiologically** acceptable metal salts. Such salts may be made from aluminum, calcium, lithium, magnesium, potassium, sodium, and zinc. Preferred organic salts can be made from ~~**tertiary**~~ amines ~~**and quaternary amine salts**~~, such as tromethamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, ~~**choline,**~~ diethanolamine, ethylenediamine, meglumine (N-methylglucamine), and procaine. Basic nitrogen-containing groups can be quaternized with agents such as lower alkyl (C_1-C_6) halides (*e.g.,* methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides), dialkyl sulfates (*e.g.,* dimethyl, diethyl, dibuytl, and diamyl sulfates), long chain halides (*e.g.,* decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides), aralkyl halides (*e.g.,* benzyl and phenethyl bromides), and others.

Paragraph 78 bridging page 26 has been amended in the following manner:

[78] A wide variety of methods may be used alone or in combination to administer the ~~**hydroxamates**~~ **hydroxamic acids** and salt thereof described above. For example, the ~~**hydroxamates**~~ **hydroxamic acids** or salts thereof may be administered orally, parenterally, by inhalation spray, rectally, or topically. Oral administration can be advantageous if, for example, the patient is ambulatory, not hospitalized, and physically able and sufficiently responsible to take drug at the required intervals. This may be true even if the person is being treated with more than one drug for one or more diseases. On the other hand, IV drug administration can be advantageous in, for example, a hospital setting where the dose (and thus the blood levels) can be well controlled. A compound or salt of this invention also can be formulated for IM administration if desired. This route of administration may be desirable for administering prodrugs or regular drug delivery to patients that are either physically weak or have a poor compliance record or require constant drug blood levels.

Paragraph 79 bridging pages 26 and 27 has been amended in the following manner:

[79] Typically, a compound (or pharmaceutically acceptable salt thereof) described in this patent is administered in an amount effective to inhibit a target MMP(s) **or aggrecanase**. The target MMP is/are typically MMP-2, MMP-9, and/or MMP-13, with MMP-13 often being a particularly preferred target. The preferred total daily dose of the ~~hydroxamate~~ **hydroxamic acid** or salt thereof (administered in single or divided doses) is typically from about 0.001 to about 100 mg/kg, more preferably from about 0.001 to about 30 mg/kg, and even more preferably from about 0.01 to about 10 mg/kg (*i.e.*, mg ~~hydroxamate~~ **hydroxamic acid** or salt thereof per kg body weight). Dosage unit compositions can contain such amounts or submultiples thereof to make up the daily dose. In many instances, the administration of the compound or salt will be repeated a plurality of times. Multiple doses per day typically may be used to increase the total daily dose, if desired.

Paragraph 80 on page 27 has been amended in the following manner:

[80] Factors affecting the preferred dosage regimen include the type, age, weight, sex, diet, and condition of the patient; the severity of the pathological condition; the route of administration; pharmacological considerations, such as the activity, efficacy, pharmacokinetic, and toxicology profiles of the particular ~~hydroxamate~~ **hydroxamic acid** or salt thereof employed; whether a drug delivery system is utilized; and whether the ~~hydroxamate~~ **hydroxamic acid** or salt thereof is administered as part of a drug combination. Thus, the dosage regimen actually employed can vary widely, and, therefore, can deviate from the preferred dosage regimen set forth above.

Paragraph 81 on page 27 has been amended in the following manner:

[81] This invention also is directed to pharmaceutical compositions comprising a ~~hydroxamate~~ **hydroxamic acid** or salt thereof described above, and to methods for making **pharmaceutical** ~~pharmacetucal~~ compositions (or medicaments) comprising a ~~hydroxamate~~ **hydroxamic acid** or salt thereof described above.

Paragraph 83 bridging pages 27 and 28 has been amended in the following manner:

[83] Solid dosage forms for oral administration include, for example, capsules, tablets, pills, powders, and granules. In such solid dosage forms, the ~~**hydroxamates**~~ **hydroxamic acids** or salts thereof are ordinarily combined with one or more adjuvants. If administered *per os*, the ~~**hydroxamates**~~ **hydroxamic acids** or salts thereof can be mixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlled-release formulation, as can be provided in a dispersion of the ~~**hydroxamate**~~ **hydroxamic acid** or salt thereof in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms also can comprise buffering agents, such as sodium citrate, or magnesium or calcium carbonate or bicarbonate. Tablets and pills additionally can be prepared with enteric coatings.

Paragraph 86 bridging pages 28 and 29 has been amended in the following manner:

[86] Formulations for parenteral administration may, for example, be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The ~~**hydroxamates**~~ **hydroxamic acids** or salts thereof can be dissolved in water, polyethylene glycol, propylene glycol, ethanol, com oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers.

Paragraph 134 bridging pages 38 and 39 has been amended in the following manner:

[134] Examples of single-ring heterocyclyls and heteroaryls include furanyl, dihydrofurnayl, tetradydrofurnayl, thiophenyl (also known as "thiofuranyl"), dihydrothiophenyl, tetrahydrothiophenyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxathiazolyl, oxadiazolyl (including 1,2,3-oxadiazolyl,

1,2,4-oxadiazolyl (also known as "azoximyl"), 1,2,5-oxadiazolyl (also known as "furazanyl"), **and [[or]]** 1,3,4-oxadiazolyl), oxatriazolyl (including 1,2,3,4-oxatriazolyl **and [[or]]** 1,2,3,5-oxatriazolyl), dioxazolyl (including 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, **and [[or]]** 1,3,4-dioxazolyl), ~~**oxathiazolyl, oxathiolyl,**~~ oxathiolanyl, pyranyl (including 1,2-pyranyl **and [[or]]** 1,4-pyranyl), dihydropyranyl, pyridinyl ~~**(also known as "azinyl"),**~~ piperidinyl, diazinyl (including pyridazinyl (also known as "1,2-diazinyl"), pyrimidinyl (also known as "1,3-diazinyl"), **and [[or]]** pyrazinyl (also known as "1,4-diazinyl")), piperazinyl, triazinyl (including s-triazinyl (also known as "1,3,5-triazinyl"), as-triazinyl (also known 1,2,4-triazinyl), and v-triazinyl (also known as "1,2,3-triazinyl")), oxazinyl (including 1,2,3-oxazinyl, 1,3,2-oxazinyl, 1,3,6-oxazinyl (also known as "pentoxazolyl"), 1,2,6-oxazinyl, **and [[or]]** 1,4-oxazinyl), isoxazinyl (including o-isoxazinyl **and [[or]]** p-isoxazinyl), oxazolidinyl, isoxazolidinyl, oxathiazinyl (including 1,2,5-oxathiazinyl **and [[or]]** 1,2,6-oxathiazinyl), oxadiazinyl (including 1,4,2-oxadiazinyl **and [[or]]** 1,3,5,2-oxadiazinyl), morpholinyl, azepinyl, oxepinyl, thiepinyl, and diazepinyl.

Paragraph 135 bridging pages 39 and 40 has been amended in the following manner:

[135] Examples of heterocyclyl and heteroaryl rings having 2 or 3 rings fused together include, for example, indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, ~~**naphthyridinyl,**~~ pyridopyridinyl (including pyrido[3,4-b]-pyridinyl, pyrido[3,2-b]-pyridinyl, **[[or]]** pyrido[4,3-b]-pyridinyl**, and naphthyridinyl**), and pteridinyl. Other examples of fused-ring heterocyclyls include benzo-fused heterocyclyls, such as indolyl, isoindolyl ~~**(also known as "isobenzazolyl" or "pseudoisoindolyl")**~~, indoleninyl (also known as "pseudoindolyl"), isoindazolyl (also known as "benzpyrazolyl"), benzazinyl (including quinolinyl (also known as "1-benzazinyl") **and [[or]]** isoquinolinyl (also known as "2-benzazinyl")), phthalazinyl, quinoxalinyl, ~~**quinazolinyl,**~~ benzodiazinyl (including cinnolinyl (also known as "1,2-benzodiazinyl") **and [[or]]** quinazolinyl (also known as "1,3-benzodiazinyl")), benzopyranyl (including **chromenyl and isochromenyl** ~~**"chromanyl" or "isochromanyl"**~~), benzothiopyranyl (also known as **thiochromenyl** ~~**"thiochromanyl"**~~), benzoxazolyl, indoxazinyl (also known as "benzisoxazolyl"), anthranilyl, benzodioxolyl,

benzodioxanyl, benzoxadiazolyl, benzofuranyl (also known as "coumaronyl"), isobenzofuranyl, benzothienyl (also known as "benzothiophenyl", "thionaphthenyl", or "benzothiofuranyl"), isobenzothienyl (also known as "isobenzothiophenyl", "isothionaphthenyl", or "isobenzothiofuranyl"), benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl (including 1,3,2-benzoxazinyl[[ ]], 1,4,2-benzoxazinyl[[ ]], 2,3,1-benzoxazinyl[[ ]], **and** **[[or]]** 3,1,4-benzoxazinyl[[ ]]), benzisoxazinyl (including 1,2-benzisoxazinyl **and** **[[or]]** 1,4-benzisoxazinyl), tetrahydroisoquinolinyl[[ ]], carbazolyl, xanthenyl, and acridinyl.

Paragraph 136 on page 40 has been amended in the following manner:

[136] As may be seen in the preceding paragraphs, the term "heteroaryl" includes 6-membered ring substituents such as ~~**pyridyl, pyrazyl,**~~ **pyridinyl, pyrazinyl,** pyrimidinyl, **[[and]]** pyridazinyl**, and 1,3,5-, 1,2,4- and 1,2,3-triazinyl**; 5-membered ring substituents such as ~~**1,3,5-, 1,2,4- or 1,2,3-tiiazinyl, imidazyl**~~, **imidazolyl,** furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-, 1,2,4-, 1,2,5-, **and** **[[or]]** 1,3,4-oxadiazolyl, and isothiazolyl; 6/5-membered fused ring substituents such as benzothiofuranyl, isobenzothiofuranyl, benzisoxazolyl, benzoxazolyl, purinyl, and anthranilyl; and 6/6-membered fused rings such as ~~**1,2-, 1,4-, 2,3- and 2, 1-benzopyronyl,**~~ quinolinyl, isoquinolinyl, cinnolinyl, **and** quinazolinyl, ~~**and 1,4-benzoxazinyl**~~.

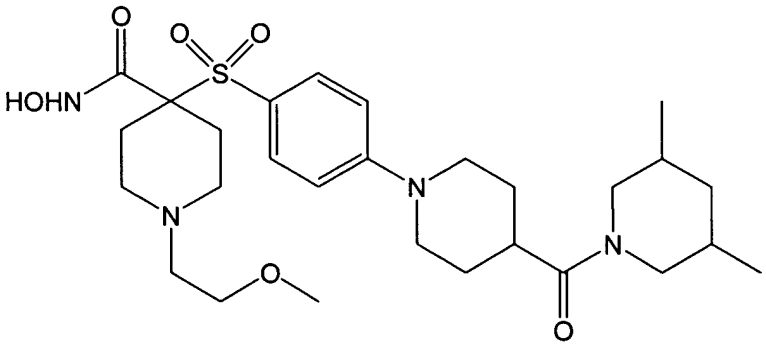
Paragraph 138 bridging pages 40 and 41 has been amended in the following manner:

[138] An aryl or heteroaryl optionally can be substituted with, for example, one or more substituents independently selected from the group consisting of halogen, -OH, -CN, -NO_2, -SH, -C(O)-OH, amino, aminocarbonyl, aminoalkyl, alkyl, alkylthio, carboxyalkylthio, alkylcarbonyl, alkylcarbonyloxy, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkoxy, alkoxyalkylthio, alkoxycarbonylalkylthio, carboxyalkoxy, alkoxycarbonylalkoxy, carbocyclyl, carbocyclylalkyl, carbocyclyloxy, carbocyclylthio, carbocyclylalkylthio, carbocyclylamino, carbocyclylalkylamino, carbocyclylcarbonylamino, carbocyclylcarbonyl, carbocyclylalkyl, ~~**carbonyl,**~~ carbocyclylcarbonyloxy, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, carbocyclyloxyalkoxycarbocyclyl, carbocyclylthioalkylthiocarbocyclyl,

carbocyclylthioalkoxycarbocyclyl, carbocyclyloxyalkylthiocarbocyclyl, heterocyclyl, heterocyclylalkyl, heterocyclyloxy, heterocyclylthio, heterocyclylalkylthio, heterocyclylamino, heterocyclylalkylamino, heterocyclylcarbonylamino, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, heterocyclyloxycarbonyl, heterocyclylcarbonyloxy, heterocyclylalkoxycarbonyl, heterocyclyloxyalkoxyheterocyclyl, heterocyclylthioalkylthioheterocyclyl, heterocyclylthioalkoxyheterocyclyl, and heterocyclyloxyalkylthioheterocyclyl. More typically, an aryl or heteroaryl may, for example, optionally be substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -CN, $-NO_2$, -SH, -C(O)-OH, amino, aminocarbonyl, amino-C_1-C_6-alkyl, C_1-C_6-alkyl, C_1-C_6-alkylthio, carboxy-C_1-C_6-alkylthio, C_1-C_6-alkylcarbonyl, C_1-C_6-alkylcarbonyloxy, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxycarbonyl, C_1-C_6-alkoxycarbonyl-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkylthio, C_1-C_6-alkoxycarbonyl-C_1-C_6-alkylthio, carboxy-C_1-C_6-alkoxy, C_1-C_6-alkoxycarbonyl-C_1-C_6-alkoxy, aryl, aryl-C_1-C_6-alkyl, aryloxy, arylthio, aryl-C_1-C_6-alkylthio, arylamino, aryl-C_1-C_6-alkylamino, arylcarbonylamino, arylcarbonyl, aryl-C_1-C_6-alkylcarbonyl, arylcarbonyloxy, aryloxycarbonyl, aryl-C_1-C_6-alkoxycarbonyl, aryloxy-C_1-C_6-alkoxyaryl, arylthio-C_1-C_6-alkylthioaryl, arylthio-C_1-C_6-alkoxyaryl, aryloxy-C_1-C_6-alkylthioaryl, cycloalkyl, cycloalkyl-C_1-C_6-alkyl, cycloalkyloxy, cycloalkylthio, cycloalkyl-C_1-C_6-alkylthio, cycloalkylamino, cycloalkyl-C_1-C_6-alkylamino, cycloalkylcarbonylamino, cycloalkylcarbonyl, cycloalkyl-C_1-C_6-alkylcarbonyl, cycloalkylcarbonyloxy, cycloalkyloxycarbonyl, cycloalkyl-C_1-C_6-alkoxycarbonyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryloxy, heteroarylthio, heteroaryl-C_1-C_6-alkylthio, heteroarylamino, heteroaryl-C_1-C_6-alkylamino, heteroarylcarbonylamino, heteroarylcarbonyl, heteroaryl-C_1-C_6-alkylcarbonyl, heteroaryloxycarbonyl, heteroarylcarbonyloxy, and heteroaryl-C_1-C_6-alkoxycarbonyl. Here, one or more hydrogens bound to a carbon in any such group may, for example, optionally be replaced with halogen. In addition, the cycloalkyl, aryl, and heteroaryl are typically single-ring groups containing 3 to 6 ring atoms, and more typically 5 or 6 ring atoms.

Paragraph 277 on page 87 has been amended in the following manner:

[277] Example 71: Preparation of 4-[[4-[4-[(3,5-dimethyl-1-piperidinyl)carbonyl]-1-piperidinyl]-phenyl]sulfonyl]-N-hydroxy-1-(2-methoxyethyl)-4-piperidinecarboxamide



A solution of the ~~**hydroxamate**~~ **hydroxamic acid** of Example 70, part F (50 mg, 0.08 mmol) in water (2 mL) was neutralized with saturated sodium bicarbonate. The aqueous solution was extracted with ethyl acetate. Concentration *in vacuo* provided the ~~**hydroxamate**~~ **hydroxamic acid** free base as an orange solid (35 mg, 75%).

Paragraph 328 on page 140 has been amended in the following manner:

[328] Several ~~**hydroxamates**~~ **hydroxamic acids** and salts thereof were assayed for MMP inhibition activity by an *in vitro* assay generally following the procedures outlined in Knight et al., *FEBS Lett.*, 296(3), 263 (1992).

Paragraph 329 on page 140 has been amended in the following manner:

[329] Recombinant human MMP-1, MMP-2, MMP-9, MMP-13, and MMP-14 were used in this assay. These enzymes were prepared in the Assignee's laboratories following usual laboratory procedures. Specifics for preparing and using these enzymes can be found in the scientific literature describing these enzymes. *See, e.g., Enzyme Nomenclature* (Academic Press, San Diego, CA, 1992) (and the citations therein). *See also*, **Freije [[Frije]]** et al., *J Biol. Chem.*, **[[26]]** **269**(24), 16766-**16773** **[[73]]** (1994).

Paragraph 333 on page 141 has been amended in the following manner:

[333] The MMP-13 was obtained as a proenzyme from a full-length cDNA clone using baculovirus, as described by V.A. Luckow, "Insect Cell Expression Technology," *Protein*

Engineering: Principles and Practice, pp. 183-218 (edited by J.L. Cleland et al., Wiley-Liss, Inc., 1996). The expressed proenzyme was first purified over a heparin agarose column, and then over a chelating zinc chloride column. The proenzyme was then activated by APMA for use in the assay. Further details on baculovirus expression systems may be found in, for example, Luckow et al., *J. Virol.*, 67**(8)**, 4566-79 (1993). *See also*, O'Reilly et al, *Baculovirus Expression Vectors: A Laboratory Manual* (W.H. Freeman and Co., New York, NY, 1992). *See also*, King et al., *The Baculovirus Expression System: A Laboratory Guide* (Chapman & Hall, London, England, 1992).

Paragraph 335 bridging pages 141 and 142 has been amended in the following manner:

[335] The subject ~~**hydroxamate**~~ **hydroxamic acid** (or salt thereof) was dissolved at various concentrations using 1% dimethyl sulfoxide (DMSO) in a buffer containing 100 mM Tris-HCl, 100 mM NaCl, 10 mM $CaCl_2$, and 0.05% polyethyleneglycol (23) lauryl ether at a pH of 7.5. These solutions were then compared to a control (which contained equal amount of DMSO/buffer solution, but no ~~**hydroxamate**~~ **hydroxamic acid** compound) using Microfluor™ White Plates (Dynatech, Chantilly, VA). Specifically, The MMPs were activated with APMA or trypsin. Then the various ~~**hydroxamate**~~ **hydroxamic acid** /DMSO/buffer solutions were incubated in separate plates at room temperature with the activated MMP and 4 um of the MMP substrate. The control likewise was incubated at room temperature in separate plates with the MMP and 4 uM of the MMP substrate. In the absence of inhibitor activity, a fluorogenic peptide was cleaved at the gly-leu peptide bond of the substrate, separating the highly fluorogenic peptide from a 2,4-dinitrophenyl quencher, resulting in an increase of fluorescent intensity (excitation at 328 nm/emission at 415). Inhibition was measured as a reduction in fluorescent intensity as a function of inhibitor concentration using a Perkin Elmer (Norwalk, CT) L550 plate reader. The IC_{50}'s were then calculated from these measurements. The results are set forth in the following Table A.

Paragraph 337 on page 154 has been amended in the following manner:

[337] The study of angiogenesis depends on a reliable and reproducible model for the stimulation and inhibition of a neovascular response. The corneal micropocket assay provides such a model of angiogenesis in the cornea of a mouse. *See*, **Kenyon, B. M., et al.**, "A Model of Angiogenesis in the Mouse Cornea" ~~; Kenyon,BM, et al.~~, Investigative Ophthalmology & Visual Science, ~~July 1996~~ **pp. 1625-1632**, Vol. 37, No. 8 **(July 1996)**.

Paragraph 389 bridging pages 162 and 163 has been amended in the following manner:

[389] Another assay for measuring aggrecanase inhibition has been reported in WIPO Int'l Publ. No. WO 00/59874. That assay reportedly uses active aggrecanase accumulated in media from stimulated bovine cartilage (BNC) or related cartilage sources and purified cartilage aggrecan monomer or a fragment thereof as a substrate. Aggrecanase is generated by stimulation of cartilage slices with interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α), or other stimuli. To accumulate BNC aggrecanase in culture media, cartilage reportedly is first depleted of endogenous aggrecan by stimulation with 500 ng/ml human recombinant IL-β for 6 days with media changes every 2 days. Cartilage is then stimulated for an additional 8 days without media change to allow accumulation of soluble, active aggrecanase in the culture media. To decrease the amounts of matrix metalloproteinases released into the media during aggrecanase accumulation, agents which inhibit MMP-1, -2, -3, and -9 biosynthesis are included during stimulation. This BNC conditioned media containing aggrecanase activity is then used as the source of aggrecanase for the assay. Aggrecanase enzymatic activity is detected by monitoring production of aggrecan fragments produced exclusively by cleavage at the Glu373-Ala374 bond within the aggrecan core protein by Western analysis using the monoclonal antibody, BC-3 (Hughes, et al., *Biochem J*, **[[306]] 305(3)**:799-804 (1995)). This antibody reportedly recognizes aggrecan fragments with the N-terminus, 374ARGSVIL, generated upon cleavage by aggrecanase. The BC-3 antibody reportedly recognizes this neoepitope only when it is at the N-terminus and not when it is present internally within aggrecan fragments or within the aggrecan protein core. Only products produced upon cleavage by aggrecanase reportedly are detected. Kinetic studies using this assay reportedly yield a Km of 1.5+/-0.35 μM for aggrecanase. To

evaluate inhibition of aggrecanase, compounds are prepared as 10 mM stocks in DMSO, water, or other solvents and diluted to appropriate concentrations in water. Drug (50 μL) is added to 50 μL of aggrecanase-containing media and 50 μL of 2 mg/ml aggrecan substrate and brought to a final volume of 200 μL in 0.2 M Tris, pH 7.6, containing 0.4 M NaCl and 40 mM $CaCl_2$. The assay is run for 4 hr at 37°C, quenched with 20 mM EDTA, and analyzed for aggrecanase-generated products. A sample containing enzyme and substrate without drug is included as a positive control and enzyme incubated in the absence of substrate serves as a measure of background. Removal of the glycosaminoglycan side chains from aggrecan reportedly is necessary for the BC-3 antibody to recognize the ARGSVIL epitope on the core protein. Therefore, for analysis of aggrecan fragments generated by cleavage at the Glu373-Ala374 site, proteoglycans and proteoglycan fragments are enzymatically deglycosylated with chondroitinase ABC (0.1 units/10 μg GAG) for 2 hr at 37°C and then with keratanase (0.1 units/10 μg GAG) and keratanase II (0.002 units/10 μg GAG) for 2 hr at 37°C in buffer containing 50 mM sodium acetate, 0.1 M Tris/HCl, pH 6.5. After digestion, aggrecan in the samples is precipitated with 5 volumes of acetone and resuspended in 30 μL of Tris glycine SDS sample buffer (Novex) containing 2.5% beta mercaptoethanol. Samples are loaded and then separated by SDS-PAGE under reducing conditions with 4-12% gradient gels, transferred to nitrocellulose and immunolocated with 1:500 dilution of antibody BC3. Subsequently, membranes are incubated with a 1:5000 dilution of goat anti-mouse IgG alkaline phosphatase second antibody and aggrecan catabolites visualized by incubation with appropriate substrate for 10-30 minutes to achieve optimal color development. Blots are quantitated by scanning densitometry and inhibition of aggrecanase determined by comparing the amount of product produced in the presence versus absence of compound.

The abstract on page 195 has been amended in the following manner:

This invention is directed to aromatic sulfone **hydroxamic acids (including** hydroxamates**)** ~~**(also known as aromatic sulfone hydroxamic acids)**~~ and salts thereof that, *inter alia,* tend to inhibit matrix metalloproteinase (also known as matrix metalloprotease or MMP) activity and/or aggrecanase activity. This invention also is directed to a treatment method that comprises administering such a compound or salt in an MMP-inhibiting and/or aggrecanase-

inhibiting effective amount to an animal, particularly a mammal having (or disposed to having) a pathological condition associated with MMP activity and/or aggrecanase activity.

CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8

I certify that this correspondence is being deposited with the U.S. Postal Service on **December 8, 2003** with sufficient postage as first class mail (including Express Mail per MPEP §512), and addressed to **Mail Stop Patent Application, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450**.

DMG/PML